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Ivor R. Elrifi
Mintz, Levin, Cohn, Ferris.
Glovsky and Popeo, P.C.
One Financial Center
Boston, MA 02111

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MYERS, CARLA J	
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SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,029	NICKLIN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *2-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/24/04 and 11/17/03* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I and the IL-1A (+4845) allele in the reply filed on October 16, 2006 is acknowledged.

Claim 1 reads on the elected invention of methods for detecting the IL-1A (+4845) allele. Claims 2-8 of Group I do not read on the elected invention because these claims require the detection of two or more alleles. Accordingly, claims 2-8 and claims 9-39 (Groups II-IV) are withdrawn from consideration as being drawn to a non-elected invention.

Claim Objections

2. Claim 1 is objected to because it encompasses the non-elected subject matter of the additional alleles (i.e., alleles other than the IL-1A (+4845) allele) set forth in Figures 1, 2A, 2B, 7A and 7B. In response to this Office action, the claims should be amended so that they are limited to the elected subject matter.

Drawings

3. Acknowledgement is made of the new drawings filed on April 22, 2004. However, Figure 18F is not acceptable. A new corrected drawings in compliance with 37 CFR 1.121(d) is required in this application because the handwritten notations for the sequences are not readable. The drawings should not be corrected by crossing through/ writing over numbers. Also, the term "SEQ ID NO: " should appear prior to each of the listed sequence identifiers.

Additionally, originally filed Figures 7A and 7B appear to be incomplete in that some of the text is not readable. See, for example, sentence 1 and 2 of Figure 7A and lines 1 and 3 of Figure 7B.

Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Priority

4. Claim 1 is entitled to priority only to U.S. application 10/351,702, filed January 27, 2003. Priority application 60/361,951, filed January 25, 2002 does not appear to provide support for the presently claimed invention of a method for determining whether a subject is predisposed to developing any disease or condition associated with an inflammatory haplotype by assaying for a IL-1A +4845 allele.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected over the recitation of "an IL-1 allele as shown in any of Figures 1, 2A, 2B, 7A or 7B." The elected invention is drawn to the detection of the IL-

1A (+4845) allele. However, this allele does not appear to be recited in Figures 1, 2A, 2B, 7A or 7B. In the response filed October 16, 2006, Applicants state that they elect invention I, IL-1A (+4845) and that this allele is recited in Figures 3A, 4A and 5A. However, claim 1 does not refer to an allele from Figures 3A, 4A or 5A. Accordingly, with respect to the elected invention, it is unclear as to what is intended to be meant by "an IL-1 allele as shown in any of Figures 1, 2A, 2B, 7A or 7B."

Claim 1 is indefinite because the claim does not recite a clear nexus between the preamble of the claim and the final step of the claim. The claim is drawn to a method for determining whether a subject is predisposed to developing a disease or condition associated with an IL-1 inflammatory haplotype. However, the claim recites only a single step of detecting an IL-1 allele. The claim does not set forth how detection of an IL-1 allele results in the determination of whether a subject is predisposed to developing a disease or condition associated with an IL-1 inflammatory haplotype. Accordingly, it is unclear as to whether the claim is intended to be limited to methods of determining whether a subject is predisposed to developing a disease or condition associated with an IL-1 inflammatory haplotype or methods for detecting an IL-1 allele.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claim 1 is drawn broadly to encompass methods for determining whether a subject has or is predisposed to developing any disease or condition that is associated with any IL-1 inflammatory haplotype comprising detecting the presence of an IL-1A (+4845) allele.

Claim 1 does not define the IL-1 inflammatory haplotype and does not recite any particular disease or condition that is associated with the IL-1 inflammatory haplotype. As discussed on pages 9-11 of the specification, diseases associated with an inflammatory haplotype may include such highly diverse diseases such as Systemic Inflammatory Response, Alzheimer's Disease, amylotropic lateral sclerosis, arthritis, asthma, cardiovascular diseases such atherosclerosis, single vessel coronary artery disease, fragile plaque disorder, congenital heart disease, cardiomyopathies, pericarditis, stroke, cardiac hypoxia, autoimmune diabetes, diabetic retinopathy diabetes, and diabetic nephropathy, gastrointestinal inflammations, gastric ulcers,

hepatic inflammations, cholesterol gallstones and hepatic fibrosis, HIV, Kawasaki's Syndrome, multiple sclerosis, neurodegenerative diseases, pulmonary diseases, osteoporosis, periodontal disease, pancreatic, chronic sinusitis, hypoxia, restenosis, resistance to infectious diseases, low birth weight, response to trauma, cancer, and fertility. These diseases differ from one another significantly with respect to their etiologies and symptomologies.

Nature of the Invention

The claims encompass methods for determining whether a subject has an increased risk of developing a disease or condition associated with an inflammatory haplotype by detecting a IL-1A (+4845) allele. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification (page 49) teaches the results of a prospective cohort study of subjects ages 45-64 having atherosclerosis. The study found that in individuals having a total cholesterol level of <200 mg/dl, there was an association between IL-1 (+4845) allele 2 and unspecified "clinical events." The specification (page 49) states that key aspects of the findings include the finding that the "+4845 genotype [is] significantly associated with clinical events (Survival Analysis Relative Risk ~ 4.0, p<.01)." Based on these teachings, it is unclear as to whether the "clinical events" referred to in the specification are intended to be limited to patient survival. It is also unclear as to

whether the association was found only in subjects homozygous for the +4845 allele 2, or was also found in subjects heterozygous for the +4845 allele 2. Thereby, the results of this study cannot be fully evaluated.

At page 51, the specification provides the results of a study of women of European/Caucasian origin having osteoporotic fractures. It is stated that in this cohort, women homozygous for IL-1A +4845 allele 2 showed an increased risk of early death from cardiovascular disease. However, the specification does not characterize the types of cardiovascular diseases present in these subjects. Cardiovascular disease covers a very broad spectrum of diseases, which differ with respect to their etiologies and symptomologies. The results obtained with one type of cardiovascular disease cannot be extrapolated to other types of cardiovascular disease. Without information regarding the particular types of cardiovascular diseases present in these subjects, the data from this study cannot be fully evaluated. If evidence is provided to establish the type or types of cardiovascular diseases from which these patients died, such evidence may be used to establish that the specification has enabled methods for determining whether a female subject with an osteoporotic fracture is at an increased risk for early death from a particular cardiovascular disease wherein the methods comprise obtaining a sample of nucleic acid from a female subject of European/Caucasian origin having an osteoporotic fracture, analyzing the IL-1A nucleotide sequence in the nucleic acid sample for the presence of a T or G at nucleotide position +4845, and determining that the female subject has an increased risk of early death from the particular

cardiovascular disease if the female subject is homozygous for a T at nucleotide position +4845.

The specification (page 51-52) also teaches that the +4845 polymorphism results in an alanine (allele 1) to serine (allele 2) amino acid change. In Western blotting studies, allele 1 (Ala) generated 1 band of 17 kDa, whereas allele 2 (Ser) generated 2 bands – one identical to the 17 kDa band found with allele 1, and a second band of a "slightly larger" molecular weight. The specification concludes that "there is a structural difference in the 2 variants." The specification also states that "(w)e postulate that the Ala to Ser mutation leads to differential post-translational modification of the proteins, for example differences in phosphorylation or myristolation" (see page 52). However, no evidence is provided to support such a conclusion.

In an *in vitro* transfection experiment in which fibroblast cells were transfected with cDNAs encoding for the Ala and Ser variants, cells carrying the allele 2 (Ser) variant were found to grow faster than cells carrying the allele 1 (Ala) variant. Based on this study, the specification concludes that "allele 2 is predictive of a proinflammatory haplotype" (see page 52). However, the results obtained regarding the growth rate of fibroblast cells *in vitro* are not sufficient to establish an *in vivo* role for the allele 2 variant in causing any and all inflammatory diseases.

Additionally, Van Dijk (U.S. Patent No. 6,558,905) teaches that the IL-1A +4845 allele 2 is associated with osteoporosis in female subjects. Kornman (U.S. Patent No. 6,733,967) teaches that the IL-1A +4845 allele 2 is associated with risk of having a low birth weight baby in female subjects. Francis (U.S. Patent No. 6,524,795 and PGPUB

No. 2006252055) discloses a method of diagnosing the risk of having or developing fragile plaque disorder by assaying for IL-1A +4845 allele 2. However, the specification as originally filed does not contemplate these specific embodiments. Rather, the specification as originally filed lists 3 pages of disorders which are intended to be encompassed by the phrase "disorders associated with an inflammatory haplotype" and states that one or more of the multitude of alleles disclosed in the specification may be associated with one of these disorders. There is no specific disclosure in the specification of particular alleles of IL-1A +4845 (i.e., either allele 1 or allele 2) which are associated with increased risk of osteoporosis in female subjects, increased risk of female subjects having a low birth weight, or incr4eased risk of fragile plaque disorder. Accordingly, the specification cannot be relied upon for providing support or enablement for methods of diagnosing osteoporosis in female subjects, methods for diagnosing risk of a low birth weight baby in female subjects, or methods of diagnosing risk of fragile plaque disorder by assaying for the IL-1A +4845 allele 2.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of establishing an association between a polymorphism and the occurrence of a disease or disorder is highly unpredictable. While some interleukin polymorphisms, particularly polymorphisms associated with increased interleukin production, have been found to be associated with some inflammatory diseases, there is no universal association established between the presence of these polymorphisms and the occurrence of all diseases. Thereby, the results obtained regarding an association between the +4845 polymorphism and risk of early death from

cardiovascular disease in European/Caucasian female subjects having osteoporotic fractures cannot be extrapolated to all other inflammatory diseases and all other populations. Additionally, the in vitro growth rate results obtained with the Ser and Ala variants is not sufficient to show that these variants are in fact associated with inflammation responses in vivo and that these variants of predictive of risk of any type of inflammatory disease.

The teachings of Lucentini (The Scientist. December 2004, page 20) highlights the unpredictability in the art of establishing an association between a mutation/polymorphism and the occurrence of a disease or condition. As discussed by Lucentini, reproducible association studies are "few and far between." The reference reports that "when a finding is first published linking a given gene with a complex disease, there is only roughly a one third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated. The first finding is usually 'spurious, or it is true, but it happens to be really exaggerated, ' ...there may be no way to predict which new gene-association studies will be verified with multiple replication."

The teachings of Armitage (Journal of Periodontology. 2000. 71: 164-171) emphasize the unpredictability of establishing an association between the particular allele of IL-1A +4845 allele and the occurrence of a disorder. Armitage teaches that the IL-1A +4845 polymorphism is found at a much lower frequency in the Chinese population. The IL-1A +4845 polymorphism was identified in only 17% of Chinese subjects (see page 169, col. 1). Armitage concludes that "(f)indings from the present

study bring into question the usefulness of the composite genotype of allele 2 of both IL-1A +4845 and IL-1B +3954 as a method for determining the susceptibility of Chinese patients to adult periodontitis" (page 169, col. 2).

The prior art and post-filing date art also corroborates the unpredictability in establishing an association between an IL-1 allele and disorders and in extrapolating the results obtained with one IL-1 allele to other alleles, as well as to other disorders and other ethnic groups. For instance, Rosenmann (Neuroscience Letters. 2004. 363: 131-133; see page 131) teaches that IL-1, and especially IL-1B is overexpressed in the CSF and brain of AD patients. The reference reports that "(r)ecent studies show inconsistent results for the association of the polymorphic sites in the IL-1B gene and AD." For example, while one group of investigators found an association between the –511 IL-1B polymorphism and late-onset AD, the association could not be confirmed by others (page 131). Similarly, while an association between the +3953 IL-1B polymorphism and AD was found in Europeans by 2 groups, other researchers did not find an association between this polymorphism and AD in Europeans or Japanese. Rosenmann (page 132) found that the +3953 polymorphism was not associated with AD or age of onset of AD. The authors concluded that '(t)hese inconsistent findings suggest that the association – if it exists – is not universal but may be population specific." However, the present specification provides the results of a study limited to females of European and Caucasian origin. Also, the results of the study showing a correlation between individuals with cholesterol levels <200 mg/dl and "clinical events" associated with atherosclerosis was limited to individuals in the US. The specification

does not teach a predictable means for determining a priori which additional populations will show a positive correlation between the +4845 polymorphism and early death from particular cardiovascular diseases and which will not. The specification also does not provide a predictable means for ascertaining which subtypes of a cardiovascular disease, such as atherosclerosis and congestive heart failure, will or will not be associated with a particular IL-1A (+4845) allele.

The unpredictability in establishing a correlation between an IL-1A +4845 polymorphism and the occurrence of any inflammatory disease, and particularly any cardiovascular disease, is further emphasized by the teachings of Francis et al. (U.S. Patent No. 6,210,877) , of which several of the present inventors are co-inventors. This reference (column 8) teaches that IL-1RN (VNTR) allele 2 is present in 41% of single vessel coronary artery disease patients and present in only 21% of control patients. However, this reference also teaches that there was no significant correlation between the IL-1A –889 polymorphism or the IL-1B +3954 polymorphism and single vessel coronary artery disease. The –889 and +3954 polymorphisms are part of the 44112332 haplotype containing IL-1RN (VNTR) allele 2, as well as the presently claimed +4845 allele 1 (see page 4 of the specification). Since even polymorphisms within the same haplotype are not correlated with single vessel coronary artery disease, it is unpredictable as to which other possible polymorphisms or haplotypes would be correlated with single vessel coronary artery disease. Further, Francis (column 10) teaches that while the IL-1B –511 allele 2 is associated with multiple coronary artery disease, other polymorphisms in the interleukin haplotype, including IL-1A –889, IL-1B

+3954 and IL-1RN (VNTR) were not correlated with multiple coronary artery disease. These results further establish the unpredictability of extrapolating the results obtained with members of a haplotype to specific alleles, such as the IL-1A +4845 alleles. Moreover, the difference in results observed between multiple vessel coronary artery disease and single vessel coronary artery disease is evidence of the fact that the results obtained with one type of cardiovascular disease cannot be extrapolated to other types of cardiovascular disease.

The unpredictability in establishing a correlation between an IL-1A +4845 allele and the occurrence of any inflammatory disease is also supported by the findings of Francis (PGPUB No. 20060252055). Francis (paragraph [0268]) studied the association between IL-1 alleles and carotid arterial wall thickness. Francis found that "There were no associations between the IL-1A (+4845), IL-1B (+3954) or IL-1B (-511) variants and carotid IMT in either ethnic group." Francis (paragraphs [0132-0133]) also reports that while allele 1 of IL-1A +4845 appears to be associated with risk of cardiovascular diseases associated with occlusion, allele 2 of IL-1A +4845 appears to be associated with risk of cardiovascular diseases associated with rupture of fragile plaques. However, the present specification does not provide guidance or teachings regarding the distinction between types of cardiovascular diseases that may be associated with the different alleles of IL-1A +4845.

Further, claim 1 as broadly written does not state the means by which one detects the IL-1A +4845 allele. Thereby, the claim encompasses detecting the +4845 allele by any means, including methods which indirectly detect the allele by detecting

other linked or associated alleles or by performing functional assays. However, the specification does not teach any particular activity assays which allow one to specifically detect the presence of the +4845 polymorphism. While the specification (page 4) states that the IL-1A (+4845) allele 1 is in 100% linkage disequilibrium with the IL-1A (–889) allele 1, the specification teach any additional specific individual polymorphisms which are sufficiently linked to the +4845 allele such that there presence is specifically correlated with the presence of the +4845 allele. The art of identifying additional polymorphisms that are in linkage disequilibrium or otherwise associated with another polymorphism is also highly unpredictable. Knowledge of the sequence of a wildtype gene, such as the IL-1A gene or other interleukin genes, does not allow one to immediately envision specific polymorphisms that are in full linkage disequilibrium with the +4845 polymorphism and which could be used in place of the +4845 polymorphism to diagnose an inflammatory disease. Without extensive information regarding the structure-function relationship between the IL-1A gene and other genes in the interleukin haplotype, it is highly unpredictable as to what would be the identity of additional mutant, allelic, or splice variants which would be associated with the +4845 polymorphism.

Amount of Direction or Guidance Provided by the Specification:

To identify which of the cardiovascular diseases and other types of inflammatory diseases are associated with the +4845 polymorphism would require extensive experimentation. For example, such experimentation may determining the frequency of the +4845polymorphism in a population of ethnically diverse individuals having a

specific cardiovascular disease, determining the frequency of these polymorphisms in control populations, comparing the sequences of these two populations, and then identifying variations which are present only in the affected group and not in the control group. While methods for identifying polymorphisms are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for polymorphisms that may linked to a disease or to another polymorphism. The results of performing such methodology is highly unpredictable. The specification has provided only an invitation to experiment. Additionally, the specification has not provided a predictable means for ascertaining which of the myriad of possible inflammatory diseases will be correlated with the +4845 polymorphism and in which ethnic populations such a correlation will be significant.

Working Examples:

Again, the specification teaches methods for directly analyzing the sequence of the IL-1A gene for the presence of a T or G at nucleotide position +4845. The results set forth in the specification regarding the frequency of this polymorphism in individuals in the U.S. having atherosclerosis and a cholesterol level less than 200 mg/ml cannot be fully evaluated because the "clinical events" that were analyzed in this study are not clearly described in the specification. Further, the results set forth in the specification regarding female individuals of European / Caucasian origin having osteoporotic fractures cannot be fully evaluated because the types of cardiovascular diseases present in these individuals are not adequately described in the specification. There are no additional examples provided in the specification in which the presence of the +4845

IL-1A polymorphism is used to effectively diagnose a representative number of the different types of cardiovascular disease, or a representative number of other types of inflammatory diseases, or a representative number of "clinical events" associated with such diseases. There are also no additional examples provided in which other ethnic populations are diagnosed for an inflammatory disorder by assaying for the +4845 polymorphism. Additionally, no working examples are provided in which the +4845 polymorphism is detected indirectly by assaying for a biological activity associated with the polymorphism or by assaying for other polymorphisms or haplotypes associated with the +4845 polymorphism.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide sufficient guidance to enable the skilled artisan to effectively diagnose an inflammatory disease by assaying for the presence of the +4845 polymorphism. The specification has not established a general association between this polymorphism and any type of cardiovascular disorder, or any other type of inflammatory disorder, in any ethnic population. Further, as discussed above, the art of using a polymorphism to diagnose diseases, and particularly diseases which are highly variable with respect to their etiologies, symptoms and outcomes, is highly unpredictable. Thereby, in view of this unpredictability in the art and the lack of specific guidance provided in the specification, the specification has not enabled one of skill in the art to practice methods for diagnosing any type of disease or condition associated with an IL-1 inflammatory haplotype by assaying for an IL-1A +4845 allele.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Armitage (Journal of Periodontology. 2000. 71: 164-171).

Regarding claim 1, as noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation". In the present situation, the claim language of "for determining whether a subject has or is predisposed to developing a disease or condition that is associated with an IL-1 inflammatory haplotype" is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. Thereby, the process steps are able to stand alone and therefore the preamble limitation is not accorded patentable weight. Thus, claim 1 is considered to be drawn to a method for detecting an IL-1 allele, wherein the IL-1 allele is the IL-1A (+4845) allele.

Armitage (page 166 and page 168, col. 1) teaches a method comprising the step of detecting the IL-1A (+4845) allele. Accordingly, the method of Armitage anticipates the claimed invention.

8. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Duff et al (U.S. Patent No. 6,706,478).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Duff (see, e.g., column 14) discloses methods for determining whether a subject is predisposed to developing or having a condition associated with an IL-1 inflammatory haplotype by assaying for the presence of an IL-1A +4845 allele. Accordingly, the method of Duff anticipates the claimed invention.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Duff et al (U.S. Patent No. 6,268,142).

Duff (see, e.g., column 14) discloses methods for determining whether a subject is predisposed to developing or having a condition associated with an IL-1 inflammatory haplotype by assaying for the presence of an IL-1A +4845 allele. Accordingly, the method of Duff anticipates the claimed invention.

10. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Kornman et al (U.S. Patent No. 6,733,967).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Kornman discloses methods for determining whether a female subject is predisposed to carrying a low birth weight baby comprising assaying for the presence of an IL-1A +4845 allele 2. As defined on pages 9-11 of the present specification, the condition of a female subject being predisposed to carrying a low birth weight baby constitutes a condition associated with an inflammatory haplotype. Accordingly, the method of Kornman anticipates the claimed invention.

11. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by van Dijk et al (U.S. Patent No. 6,558,905).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Van Dijk discloses methods for determining whether a female subject has or at risk of developing osteoporosis comprising assaying for the presence of an IL-1A +4845 allele 2. As defined on pages 9-11 of the present specification, the condition of osteoporosis constitutes a condition associated with an inflammatory haplotype. Accordingly, the method of van Dijk anticipates the claimed invention.

12. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Francis et al (U.S. Patent No. 6,524,795).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Francis discloses methods for determining whether a subject has or at risk of developing fragile plaque disorder comprising assaying for the presence of an IL-1A +4845 allele 2. As defined on pages 9-11 of the present specification, the condition of osteoporosis constitutes a condition associated with an inflammatory haplotype. Accordingly, the method of Francis anticipates the claimed invention.

13. Claim 1 is provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 10/843,493 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

In particular, copending application 10/843,493 discloses methods for determining whether a female subject is predisposed to carrying a low birth weight baby comprising assaying for the presence of an IL-1A +4845 allele 2. As defined on pages

9-11 of the present specification, the condition of a female subject being predisposed to carrying a low birth weight baby constitutes a condition associated with an inflammatory haplotype. Accordingly, the claimed method is anticipated by the disclosure of '493.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

14. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Francis et al (PGPUB No. 20060252055).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Francis (paragraphs [0132] and [0270]) discloses methods for determining whether a subject has or is at an risk of developing fragile plaque disorder comprising assaying for the presence of an IL-1A +4845 allele 2. As defined on pages 9-11 of the present specification, the condition of osteoporosis constitutes a condition associated

with an inflammatory haplotype. Accordingly, the method of Francis anticipates the claimed invention.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,706,478. Although the conflicting claims are not identical, they are not patentably distinct from each other. The present claims and the claims of '029 both encompass methods for determining whether a subject is predisposed to developing or having a condition associated with an IL-1 inflammatory haplotype by assaying for the presence of an IL-1 +4845 allele.

16. Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,733,967. Although the conflicting claims are not identical, they are not patentably distinct from each other. The present claims encompass methods for determining whether a subject

is predisposed to developing or having a condition associated with an IL-1 inflammatory haplotype by assaying for the presence of an IL-1A +4845 allele. The claims of '967 are limited to methods which determine whether a female subject is predisposed to carrying a low birth weight baby by assaying for the IL-1A +4845 allele 2. As defined on pages 9-11 of the present specification, the condition of a female subject being predisposed to carrying a low birth weight baby constitutes a condition associated with an inflammatory haplotype. Accordingly, the present claims are not patentably over the claims of '967.

17. Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,558,905. Although the conflicting claims are not identical, they are not patentably distinct from each other. The present claims encompass methods for determining whether a subject is predisposed to developing or having a condition associated with an IL-1 inflammatory haplotype by assaying for the presence of an IL-1A +4845 allele. The claims of '905 are limited to methods which determine whether a female subject is predisposed to osteoporosis by assaying for the IL-1A +4845 allele 2. As defined on pages 9-11 of the present specification, osteoporosis constitutes a condition associated with an inflammatory haplotype. Accordingly, the present claims are not patentably over the claims of '905.

18. Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,524,795. Although the conflicting claims are not identical, they are not patentably distinct from each other. The present claims encompass methods for determining whether a subject

is predisposed to developing or having a condition associated with an IL-1 inflammatory haplotype by assaying for the presence of an IL-1A +4845 allele. The claims of '795 are limited to methods which determine whether a subject is predisposed to fragile plaque disorder by assaying for the IL-1A +4845 allele 2. As defined on pages 9-11 of the present specification, fragile plaque disorder constitutes a condition associated with an inflammatory haplotype. Accordingly, the present claims are not patentably over the claims of '795.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Carla Myers

Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER